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The goal of this training program is to dramatically extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This track offers both MD/PhD and PhD training opportunities, and integrates new faculty from the Lombardi Cancer Center Program in Cancer Prevention and Control, and Cancer Genetics. The program is enriched by new courses, as well as practical research experience. This new programmatic initiative makes use of the existing organizational structure of the Interdisciplinary Doctoral Training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer. We recruited 3 MDs to the program in the third year. All three MDs have had a successful first year and are continuing into their second year of enrollment in the program. Two courses, Genetics Health and Society in the 21st Century and Applied Biostatistics had a successful first year and will continue to be offered. Finally, a new course in genetics, Human and Microbial Genetics, will be offered in the fall semester.

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COMBINED M.D./Ph.D. TRAINING PROGRAM IN BREAST CANCER PREVENTION

INTRODUCTION

The goal of this program is to dramatically extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This new track offers both MD/PhD and PhD training opportunities, and integrates faculty from the Lombardi Cancer Center. The program is enriched by new courses covering cancer genetics, molecular epidemiology, and cancer prevention, as well as practical research experience. This new programmatic initiative makes use of the existing organizational structure of the Interdisciplinary Doctoral Training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer.

BODY

Training and Research Accomplishments

The accomplishments of this new program in its third year fall into two categories: the recruitment and progress of trainees, and the development of courses for the program. The Interdisciplinary Doctoral Training Program in Tumor Biology recruited, under this grant, 3 new students in the current year. Rita Kralik, M.D. has come into the program with one year advanced standing in terms of prior graduate coursework. Dr. Kralik was selected into the program based on her outstanding qualifications and the compatibility of interests with the goals of this program. Dr. Kralik is currently completing her course requirements and will perform laboratory rotations in order to select a thesis research laboratory. Two additional trainees also have been recruited for the third incoming class of the Breast Cancer Prevention Track of the Interdisciplinary Doctoral Training Program in Tumor Biology: Ion Cotarla, M.D., and Riddhish Shah, M.D. Drs. Cotarla and Shah also have advanced standing from prior graduate courses and have successfully completed their first year of training and coursework and are now beginning thesis research. Dr. Cotarla is interested in cancer genetics and breast cancer, and has joined Dr. Priscilla Furth for thesis research studying regulation and function of Stat5 in normal and malignant mammary epithelial cells, and Brcal conditional knockout mouse model as a tool for evaluating tamoxifen prevention strategy in Brcal mutation carriers. Dr. Shah has successfully completed his comprehensive examination and is currently in thesis research studying a polymorphism in 5' regulatory and signal sequence region of human TGF-beta 1 and its functional importance, with Dr. Carolyn Hurley.

Three trainees had been recruited for the second incoming class of the Breast Cancer Prevention Track of the Interdisciplinary Doctoral Training Program in Tumor

Biology (see prior Annual Report): one MD/PhD candidate, Ms. Carolyn Lee, and two PhD candidates, Ms. Sonia de Assis and Mr. Elijah Herbert. Ms. de Assis has a master's degree and research experience in the field of breast cancer, and is interested in breast cancer prevention as related to diet and environment. She has successfully completed two years of training and is now starting her third year in the program. Ms. Lee has completed her first year as an MD/PhD trainee and is currently in thesis research with Dr. Todd Waldman studying cancer genetics and breast cancer. Unfortunately, Mr. Elijah Herbert withdrew from the program after only a few months for very acute health reasons; we were able to use his slot in the program for recruitment of Ms. Carolyn Lee (above).

Two trainees had been recruited into the first incoming class, Ms. Christine Coticchia and Ms. Stacey Kessler (see prior Annual Report). Ms. Coticchia has received a DOD predoctoral fellowship, she passed her comprehensive examination and is proceeding with thesis research with Dr. Robert Dickson. Unfortunately, Ms. Kessler withdrew from the program for personal reasons, but she earned a Masters degree in Tumor Biology. However, unexpected funds available due to her departure were productively used to recruit a student with advanced standing into the third (current) class.

In addition to the existing core course work of the Interdisciplinary Doctoral Training Program in Tumor Biology, new course components have been incorporated into the Breast Cancer Prevention track in Spring 2002. These include a course in Biostatistics, *Applied Biostatistics*, that has been refocused on statistical design and methodology for research rather than biostatistics theory, and a Cancer Genetics course, *Genetics, Health, and Society in the 21st Century*, which focuses on practical and ethical questions raised by genetic information and technology. Both courses had a very successful first year and will continue to be offered. A new course in Genetics, *Human and Microbial Genetics*, has been developed and will be offered in the Fall.

All of these courses emphasize breast cancer, as most of the teaching faculty are extensively involved in breast cancer research. Interest in these courses has not been limited to students in the new Breast Cancer Prevention track: a number of additional students in the Interdisciplinary Doctoral Training Program in Tumor Biology and other biomedical graduate programs at Georgetown University have enrolled as well.

KEY ACCOMPLISHMENTS

- *Recruitment of New Trainees and Advancement of Existing Trainees:*
Class # 3
 - Riddhish Shah, M.D. has completed his coursework and has successfully completed his comprehensive examination and is now in the Thesis Research portion of the program.
 - Ion Cotarla, M.D. has completed his coursework and will be taking his comprehensive examination in July 2002.

- Rita Kralik, M.D. has completed her first semester of coursework and will continue into her second and final semester of coursework in the Fall.

Class # 2

- Ms. Carolyn Lee has successfully completed coursework and her comprehensive examination and is continuing in Thesis Research.
- Ms. Sonia de Assis has completed her coursework and will be taking her comprehensive examination in the Fall.

Class # 1

- Ms. Christine Coticchia, from class #1 completed her comprehensive examination June 2001 and is currently progressing in Thesis Research.

- *New Courses:*

- A new course, *Human and Microbial Genetics*, will be offered in the fall.
- Two courses, *Applied Biostatistics* and *Genetics, Health and Society in the 21st Century* both had a very successful first semester and will continue to be offered.

REPORTABLE OUTCOMES

- *Student Publications:*

- Hruska KS, Tilli MT, Ren S, **Cotarla I**, Kwong T, Li M, Fondell JD, Hewitt JA, Koos RD, Furth PA and Flaws JA. Conditional over-expression of estrogen receptor alpha in a transgenic mouse model. *Transgenic Research*, 2002, in press.
- Hilakivi-Clarke LA, Cho E, **de Assis S**, Olivo S, Ealley E, Bouker KB, Welch JN, Khan G, Clarke R, and Cabanes A. "Maternal and prepubertal diet, mammary development and breast cancer risk." *J Nutr* 2001, 131:154-157.
- Harris VK, Kagan BL, Ray R, **Coticchia CM**, Liaudet-Cooperman ED, Wellstein A, Riegel AT. Serum induction of the fibroblast growth factor-binding protein (FGF-BP) is mediated through ERK and p38 MAP kinase activation and C/EBP-regulated transcription. *Oncogene* 2001 Mar 29;20(14):1730-8.
- Ramljak D, **Coticchia C**, Nishanian GT, Saji M, Ringel MD, Conzen SD, and Dickson RB. Epidermal growth factor inhibition of c-myc-mediated apoptosis through Akt and Erk involves Bcl-X_L upregulation. *Oncogene* (submitted).

- *Student Abstracts/Presentations:*

- Selaru FM, Xu Y, Yin J, Shustova V, Zou T, Twigg C, Abraham JM, Mori Y, Sato F, **Cotarla I**, Greenwald BD and Meltzer SJ. Microarray and bioinformatics

analyses discriminate among biologic subtypes of esophageal neoplasia. Meeting Abstract. *Gastroenterology*, 120 (5): 226, Suppl. 1, April 2001.

- **Cotarla I**, Ren S, Li M, Zhang Y, Ghehan E, Singh B and Furth PA. Stat5 is activated in human breast cancers and associates with the p85 subunit of PI-3 kinase. Poster. Georgetown University Department of Medicine Research Day, Washington, DC; April 4, 2002. Graduate Student Organization Research Day; April 16-17, 2002. Meeting Abstract. *Proc Soc Exp Biol Med*, Washington D.C. Chapter Graduate Student Research Forum, Washington, D.C.; April 2002.
- **Cotarla I**, Ren S, Li M, Khan GA, Hilakivi-Clarke LA and Furth PA. Regulation and function of activated Stat5 in normal and malignant mammary epithelial cells. Poster 4th Annual Lombardi Research Fair, Washington, DC; February 19, 2002; Georgetown University 16th Annual Student Research Day, Washington, DC; February 21, 2002.
- **de Assis S**, Ambrosone, CB, Wustrack, S, Krishnan, S, Frudenheim, JL, Shields, PG. Microsomal epoxide hydrolase polymorphisms and tobacco smoking in relation to risk of breast cancer. *American Association for Cancer Research*, San Francisco, CA, 2002.
- **de Assis S**, Ambrosone CB, Wustrack S, Krishnan S, Freudenheim JL, Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.
- **de Assis S**, and Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. 4th Annual Lombardi Research Fair. Georgetown University Medical Center, Washington, D.C. 2002.
- **Coticchia CM**, and Dickson RB. The role of c-Myc overexpression in sensitization of mammary epithelial cells to apoptosis. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.
- Ramljak D, **Coticchia CM**, Nishanian TG, and Dickson RB, AKT inhibits c-Myc-mediated apoptosis in mammary epithelial cells: a mechanistic investigation. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.
- **Coticchia CM**, Wang J-K, Dickson R. Evaluation of pathways involved in C-Myc-induced apoptosis of mouse mammary carcinoma cells. 4th Annual Lombardi Research Fair. Georgetown University Medical Center, Washington, D.C. 2002.
- **Lee C**, Waldman T. Functional Analysis of PTEN in Human Cancer Cells by Human Somatic Cell Gene Targeting. 4th Annual Lombardi Research Fair. Georgetown University Medical Center, Washington, D.C. 2002

CONCLUSIONS

The goal of this training program is to dramatically extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. Additionally, new course components have been incorporated into the Breast Cancer Prevention track that focus on cancer genetics, cancer prevention, and epidemiology and cancer risk.